REMARKS/ARGUMENTS

Status of Claims

Claims 1, 9-14 and 21-26 are pending in the application. Claims 9 and 21-26 were subject to restriction and/or election requirement and have been withdrawn. Claims 1 and 10 have been amended. Claims, 2-8, and 15-20 have been canceled.

Status of Withdrawn Claims

Applicants' attorney respectfully submits that claims 15-20 were canceled in favor of rewritten claims 21-26. Consequently claims 21-26 are also subject to rejoinder, if the claims to the elected invention are found allowable.

Amendments to the Claims

Claims 1 and 10 have been amended to clarify the claimed invention. Claim 1 has been amended to clarify the effective amount treat respiratory depression caused by opioids. This amendment is supported by the disclosure in the specification such as by example C3. Claim 10 was amended to correct certain typographic mistakes. These amendments are submitted to clarify what applicant regards as his invention and does not introduce new matter into the claim. Applicant reserves the right to present the subject matter removed from these claims in a continuation application. Accordingly consideration and entry of this amendment is requested.

Rejection under 35.U.S.C. §103

1. Claims 1-8 and 10-14 have been rejected under 35 U.S.C. §103 as being unpatentable over WO 97/25988 (Iyengar et al.) in view of US patent 6,197,772 B1 (Janssens et al.).

Iyengar et al. describes the combination of a specific tachykinin receptor antagonist with analgesics for the treatment of pain or prevention of pain or nociception. Janssens et al., which is a significant contribution to the art, describes substance P antagonist, including the claimed compound. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-

piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing a μ-opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Example C3 describes a test of the claimed compound in combination with an opioid in three different animal models gerbils, guinea pigs and rats. The data on gerbils indicated that the claimed compound reduced part of the respiratory depression induced by opioids. Opioid excitation is believed to be one of the mechanisms of respiratory depression. However, in two of the animals tested (guinea pigs and rats) opioids do not cause excitation. These two animals also showed reduced respiratory depression when treated with opioids (See Example C3, pages 53, line 29 et seq.). These experimental results provide a comparison both with and without the claimed compound. Therefore, applicants respectfully submit that the comparative examples are already present. In view of the amendments to the claims, applicants respectfully submit that the claims are now commensurate in scope with the showing that has been made.

Applicants' attorney respectfully submits that neither, Iyengar et al. or Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants submit that an appropriate showing has been made and that the claims distinguish over the art of record and are in condition for allowance.

2. Claims 1-8 and 10-13 have been rejected under 35 U.S.C. §103 as being unpatentable over US patent 5,880,132 (Hill) in view of US patent 6,197,772 B1 (Janssens et al.). However, applicants' attorney respectfully requests reconsideration of this rejection.

Hill describes tachykinin antagonist and opioid for treating pain or nociception. Janssens et al., which is a significant contribution to the art, describes substance P antagonists, including the

claimed compound. Hill, however, does indicates in column 2, line 65 through column 3, line 3, that some of the side effects of opioid analgesic (such as respiratory depression, constipation, nausea and vomiting, etc.) can be reduced by using sub-maximal doses of the opioid analgesic. A similar point is made in column 28, lines 39-49 of Hill also discusses using reduced dosage levels of opioids. The additive effect of NK-1 receptor antagonist and opioid analgesics is further discussed in the examples in column 51, lines51-60. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy (see Example C3).

Respiratory depression appears to occur through opioids causing a μ-opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Applicants' attorney respectfully submits that neither, Hill or Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the claims as presently amended are directed to a composition that unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

3. Claims 1-8, and 10-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over US patent application publication 2002/0052504 (Elliott) in view of US 6,197,772 (Janssens et al.). However, applicants' attorney respectfully requests reconsideration of this rejection.

Elliott describes a tachykinin antagonist having a significantly different structure for the compound of the present invention. Elliott indicates on page 4, in paragraph 50 that substance P antagonists may be used in the treatment of respiratory diseases particularly those associated with excess mucus such as chronic obstructive airway disease, bronchopneumonia chronic bronchitis cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough. Elliott suggests that the compounds described therein can be combined with other analgesics such as opioids. Janessens et al., which is a significant contribution to the art, describes substance P

antagonist, including the claimed compound. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing a μ-opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Applicants' attorney respectfully submits that neither, Elliott nor Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the claims as presently amended claim a composition that unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

4. Claims 1-8, and 10-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over US patent 6,138,824 (MacLeod et al.) in view of US 6,197,772 (Janssens et al.).

MacLeod et al. describes 1-piperidinyl-propan-2-derivatives having a significantly different structure for the compound of the present invention. MacLeod et al. indicates in column 8, lines 5-10 that substance P antagonists may be used in the treatment of respiratory diseases particularly those associated with excess mucus such as chronic obstructive airway disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough. MacLeod et al. suggests that the compounds described therein can be combined with other analgesics such as opioids. Janessens et al., which is a significant contribution to the art, describes substance P antagonist, including the claimed compound. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-

(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing μ-opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Applicants' attorney respectfully submits that neither, MacLeod et al. nor Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the claims as presently amended claim a composition that unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

CONCLUSION

The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this Amendment to Deposit Account No. 10-0750/PRD2077USPCT1/HBW.

Early favorable action on the merits is respectfully requested. Applicant respectfully requests that a timely Notice of Allowance of claims 1 and 10-14.

Respectfully submitted,

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